IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Serial No.	09/118,730
Filed:	July 17, 1998
Inventors:	Ellington M. Beavers et al
Title:	METHOD OF MAKING FREE ACIDS FROM POLYSACCHARIDE SALTS
Examiner:	E. White
Art Unit:	1623
File No.:	281-28

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231, ON THE DATE INDICATED BELOW.

BY William H. Elberg

DATE 5/12/00

BRIEF FOR APPELLANTS

Appellants submit this Brief, pursuant to 37 C.F.R. §1.192. Appellants mailed the Notice of Appeal, together with a check for $150.00, on March 13, 2000. A check for $150.00, in payment of the fee required by 37 C.F.R. §1.17(c), accompanies this Brief.

I. Real Party in Interest

The present application is assigned of record to Biocoat Incorporated. The real party in interest is therefore Biocoat Incorporated.

II. Related Appeals and Interferences

The undersigned is aware of no related appeals or interferences.

III. Status of Claims

This application originally contained 23 claims. Claims 9-19 were cancelled, and Claims 1 and 20 were amended by the Amendment mailed July 13, 1999. Claims 1 and 20 were further amended by the Amendment under Rule 116, mailed February 17, 2000, and entered in the file. The claims now pending are therefore Claims 1-8 and 20-23.

The Examiner has rejected Claims 1-8 and 20-23 under 35 U.S.C. §103 as unpatentable over Schultz (U.S. Patent No. 4,808,576).

Appellants appeal from the final rejection of Claims 1-8 and 20-23.

IV. Status of Amendments

Appellants have amended this application twice, first in response to the non-final Official Action of March 15, 1999, and secondly in response to the final action of October 14, 1999. The Examiner stated, in the Advisory Action of March 10, 2000, that the amendment after final rejection would be entered upon the filing of a Notice of Appeal and an Appeal Brief.

V. Summary of the Invention

The present invention is a composition of matter, made by a defined process. All of the pending claims are product-by-process claims.

The product of the present invention is a free-acid form of hyaluronic acid which is suitable for placement permanently or temporarily in the body. For convenience, Appellants use the informal term "medical grade" to mean that the product is suitable for placement in the body.

As will be explained in more detail below, the free-acid form of hyaluronic acid is not an article of commerce, and is not commercially available anywhere. However, it has been customary, in the field, to use the term "hyaluronic acid" when what is really meant is the sodium salt, i.e. sodium hyaluronate. Therefore, when one encounters the term "hyaluronic acid" in the prior art, one must be careful to determine whether the term is used to mean the free-acid form, or the sodium salt.

The composition of the present invention is made by dissolving an

alkali-metal salt of hyaluronic acid in water, and dispersing, in the solution, an acid capable of producing a pH of 2.2 or lower, at concentrations in water at 25° C of 0.01 Normal to 1 Normal. Then, the dispersion so formed is enclosed within a semi-permeable membrane having a molecular weight cut-off at least large enough to pass the acid. The dispersion is then dialyzed in water, while enclosed within the membrane. The free hyaluronic acid is then harvested from within the membrane.

The following is a concise summary of the invention, with annotations showing the portions of the specification which support each statement.

The medical-grade hyaluronic acid of the present invention is made by the following method. First, an alkali-metal salt of hyaluronic acid is dissolved in water (page 3, lines 7-8). Then, an acid capable of producing a pH of 2.2 or lower at concentrations in water at 25° C of 0.01 Normal to 1 Normal is dispersed in the solution (page 3, lines 8-10). Next, the dispersion so made is dialyzed using a semi-permeable membrane having a molecular weight cut-off which is at least large enough to pass the added acid (page 3, lines 10-12). The final product is then harvested from inside the semi-permeable membrane (page 5, lines 1-2).

The Appendix contains a clean reproduction of all of the claims on appeal. The following reproductions of the claims on appeal include annotations which identify the pertinent portions of the specification:

1. A free-acid form of hyaluronic acid, made by the method comprising the steps of:

a) dissolving an alkali-metal salt of hyaluronic acid in water to form a solution (page 3, lines 7-8),

b) dispersing in said solution an acid capable of producing a pH of 2.2 or lower at concentrations in water at 25° C of 0.01 Normal to 1 Normal (page 3, lines 8-10),

c) enclosing the dispersion formed in step (b) within a semi-permeable membrane having a molecular weight cut-off at least large enough to pass said acid (page 3, lines 10-12),

d) dialyzing the dispersion in water while the dispersion is so enclosed (page 3, lines 10-12), and

e) harvesting free hyaluronic acid from within the semi-permeable membrane (page 3, line 12; page 4, lines 14-15; page 5, lines 1-3),

wherein the free hyaluronic acid harvested in step (e) is suitable for placement permanently or temporarily in the body (page 1, lines 17-19).

2. The product of Claim 1, wherein the membrane is chosen to be non-ionic (page 4, line 14).

3. The product of Claim 1, wherein the acid added in step (b) is an acid selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, orthophosphoric acid, and oxalic acid (page 8, lines 14-15).

4. The product of Claim 1, wherein the semi-permeable membrane is made from a material selected from the group consisting of regenerated cellulose and cellulose esters (page 8, lines 20-21).

5. The product of Claim 1, wherein the molecular weight cut-off of the semi-permeable membrane is at least twice as great as that needed to

pass the acid added in step (b) (page 8, line 22 through page 9, line 1).

6. The product of Claim 1, wherein the ratio of volume of the water used to dialyze in step (d), to the volume of the hyaluronate solution, is 5:1 or less (page 10, lines 8-10).

7. The product of Claim 1, wherein the steps are performed at a temperature in the range of about 4-30° C (page 10, line 26 through page 11, line 3).

8. The product of Claim 1, wherein the dialyzing step is performed until water surrounding the membrane has a predetermined pH (page 10, lines 11-13).

20. A free-acid form of hyaluronic acid, made by the method comprising the steps of:

a) preparing a solution of sodium hyaluronate in distilled water (page 9, lines 6-7),

b) mixing into said solution an acid capable of producing a pH of 2.2 or lower at concentrations in water at 25° C in the range of 0.01 Normal to 1 Normal, to produce a mixture (page 3, lines 8-10),

c) enclosing said mixture in a dialysis bag having a molecular weight cut-off large enough to pass the acid added in step (b) (page 3, lines 10-12),

d) placing the bag in de-ionized water (page 9, lines 16-17),

e) periodically replacing the de-ionized water with fresh de-ionized water, until the pH of the de-ionized water exceeds 5.0 (page 9, lines 18-20), and

f) harvesting free hyaluronic acid from within the bag (page 3, line 12; page 4, lines 14-15; page 5, lines 1-3),

wherein the free hyaluronic acid harvested in step (f) is suitable for placement permanently or temporarily in the body (page 1, lines 17-19).

21. The product of Claim 20, wherein the dialysis bag comprises a non-ionic membrane (page 4, line 14).

22. The product of Claim 20, wherein the acid added in step (b) is hydrochloric acid (page 4, lines 20-21).

23. The product of Claim 20, wherein the molecular weight cut-off of the bag is 3500 (page 9, line 16).

VI. Issues

This appeal presents the following single issue:

Whether the patent to Schultz renders obvious the invention claimed in Claims 1-8 and 20-23.

VII. Grouping of Claims

For purposes of this appeal, all of Claims 1-8 and 20-23 can be considered to stand or fall together.

VIII. Argument

a) Summary of Argument

The present invention is a free-acid form of hyaluronic acid, which is of medical grade, i.e. which can be safely placed in the body.

The claimed product is not commercially available. The literature is filled with misleading references to "hyaluronic acid", when what is really meant is sodium hyaluronate. This confusion of terminology persists today; some vendors still offer "hyaluronic acid", but what is sold is only the sodium salt.

Appellants' experiments have shown that it is possible to make a free-acid form of hyaluronic acid, in the laboratory, by methods shown in the prior art, but that the resulting product is not of medical grade. Thus, any reference that merely mentions "hyaluronic acid" is not enabling for the claimed product, because it is impossible to determine how the product was made and therefore whether it can be safely placed in the body.

The patent to Schultz, the only reference relied upon by the Examiner, states that the free-acid form of hyaluronic acid could be used, but admits that all of the data in the patent are based on sodium hyaluronate, not on the free-acid. Under the applicable law, the patent to Schultz is not enabling for the free-acid form of hyaluronic acid, when viewed together with the other evidence of record.

The claimed product has unexpected properties, which would not have been obvious to the person of ordinary skill. The claimed product is used in providing hydrophilic and lubricious coatings for articles to be placed in the body. It was Appellants' realization that the free-acid form of hyaluronic acid had a special (and previously unrecognized) advantage that motivated the making of the present invention.

b) Description of the References

The patent to Schultz (U.S. Patent No. 4,808,576) is the only reference relied upon by the Examiner. The Examiner does not argue that Schultz (or any other reference) discloses the process for making free hyaluronic acid described in the specification. That process has already been patented by Appellants. Rather, the Examiner's argument is that the product made by Appellants' process is not new.

The Schultz patent teaches the administration of "hyaluronic acid" to a horse or a human being, at a site remote from that of an injury. The patent teaches that the "hyaluronic acid" is transported by the body, from the site at which it is introduced, to the site of the injury, thereby enabling the material to relieve pain.

Although Schultz suggests (column 4, lines 61-62) that hyaluronic acid could be used in its free-acid form, the patent admits (column 4, line 67 through column 5, line 6) that all of the data presented in the patent, and all of the examples given in the patent, were based on sodium hyaluronate, not on free hyaluronic acid. Schultz gives no information about how to make the free-acid form of hyaluronic acid, and provides no source from which the free-acid form could be obtained. Indeed, in view of the facts discovered by Appellants (and explained in detail below), it is virtually certain that the free-acid form of hyaluronic acid was never available to Schultz. The mention of the free-acid form of hyaluronic acid, by Schultz, is mere conjecture.

Moreover, note that Schultz uses the term "hyaluronic acid" generically to refer to both the free-acid form and to its sodium and potassium salts. As will be explained in more detail below, this imprecision of terminology is common in the field.

The Examiner has also cited (in the first Official Action) the patents to de Belder (U.S. Patent No. 4,886,787), Choay (U.S. Patent No. 4,168,377), and Omiya (U.S. Patent No. 4,508,894). These references are no longer relied upon to reject the claims. Of these references, Choay and Omiya are not relevant to the claims on appeal because they do not relate to hyaluronic acid. All of the claims on appeal are specific to hyaluronic acid. The patent to de Belder purports to disclose free hyaluronic acid, but Appellants have shown that the context of the patent, plus the history of confusion of terminology in the industry, clearly indicate that only the salt form was used. As explained in the Second Declaration of Ellington M. Beavers under Rule 132 (filed with the Amendment mailed July 13, 1999), the example shown in de Belder used glacial acetic acid, which would not have been necessary if de Belder had really used the free-acid form. Moreover, de Belder does not specify how the alleged free-acid form of hyaluronic acid was made; as described below, the method of manufacture critically affects the properties of the product. De Belder therefore does not contain sufficient information to determine exactly what substance was used, and cannot be deemed to anticipate or suggest the claimed medical grade hyaluronic acid.

c) Confusion of Terminology:
References May Not Mean What They Say

A complete understanding of the issues of this appeal requires an explanation of the confusing and imprecise terminology used to describe "hyaluronic acid" in the field. For some unknown reason, it has been the custom in the field to use the term "hyaluronic acid" generically to refer to either or both of the free-acid form and to the sodium salt. The academic literature is filled with references to "hyaluronic acid" when what is really meant is "sodium hyaluronate". Sometimes, the imprecise terminology is not even recognized by those who use it.

The confusion of terminology is not limited to academic writings, but persists in the business world. As will be described below, Appellants have occasionally found vendors who purported to sell "hyaluronic acid". In every case, the product has turned out to be sodium hyaluronate, not hyaluronic acid.

The confusing and imprecise terminology used in the field of the invention is more fully documented in the Second Declaration of Ellington M. Beavers, filed under Rule 132, with the Amendment mailed July 13, 1999. Attached to that Declaration are two articles which illustrate the problem. In one article, from the Journal of Histochemistry and Cytochemistry, the author describes (on page 26) various batches of sodium or potassium salts of mucopolysaccharides. All of the substances are labeled "salts", but the hyaluronate is labeled "hyaluronic acid", while all of the other salts are correctly designated as "keratin sulfate" and "chondroitin sulfate". None of the substances described could be free acids, because the text specifies a pH at which the acid form could not exist. The above-cited article presents a graphic example of the imprecise and misleading use of the term "hyaluronic acid" when what is really meant is sodium hyaluronate.

The other article attached to Dr. Beavers' Declaration, called "The Biology of Hyaluronan" proposes the adoption of the term "hyaluronan" to identify the polysaccharide generically, so as to allow the terms "sodium hyaluronate" and "hyaluronic acid" to be used to designate the sodium salt and the free acid, respectively. However, this proposal has not been universally adopted. As noted above, the term "hyaluronic acid" is still used often, when what is meant is the sodium salt. The clear inference derived from the above-cited article is that there is a serious problem of nomenclature in the field, and that the term "hyaluronic acid" has long been used improperly and misleadingly.

The confusion in the academic literature is confirmed by the practical experiences of Appellants. Both the Second and Third Declarations of Dr. Beavers (which form part of the present record) relate some of these experiences. The Second Declaration relates how Dr. Beavers and his associates inquired of all the major chemical suppliers in the field, to determine whether free hyaluronic acid was available for sale. In all but two cases, the answer was that the suppliers could provide only the sodium salt. In the other two cases, what was advertised as the free-acid form later proved to be the sodium salt.

In the Third Declaration, filed with the Amendment mailed February 17, 2000, Dr. Beavers relates a more recent experience in which he was assured by a supplier that the free-acid form of hyaluronic acid was available. The product was ordered, but when it arrived, the certificate of analysis showed the product to be sodium hyaluronate.

It is, unfortunately, quite common, in the field of the invention, to use the term "hyaluronic acid" when what is meant is the sodium salt. Even the Schultz patent, relied upon by the Examiner, perpetuates this confusion

by adopting the term "hyaluronic acid" to refer to all forms of the mucopolysaccharide (column 5, lines 5-6).

It is quite apparent that the free-acid form of hyaluronic acid is not an article of commerce. Dr. Beavers, one of the inventors and the signatory of the above-cited declarations, is a research chemist with over a half-century of experience. If the free-acid form of hyaluronic acid had been commercially available, he would have found it. Indeed, it was the unavailability of the free-acid form which motivated the making of the present invention.

The imprecise terminology used in the literature, and in the trade, shows that, in this field, a reference does not necessarily mean what it appears to say. Some authors recognize the fact that they are using imprecise language, but still refer to the mucopolysaccharide generically as "hyaluronic acid". Others do not even recognize that there is an ambiguity. The background explained above shows that each reference must be critically evaluated before it can be concluded that a real teaching of "hyaluronic acid" exists. In summary, the mere use of the term "hyaluronic acid" in a reference does not necessarily mean that the author really used the free-acid form.

d) The Method of Making the Product Critically Affects the Properties of the Product

The claimed invention is a free-acid form of hyaluronic acid, which is suitable for placement permanently or temporarily in the body. That is, the claims on appeal require that the product be of "medical grade".

Appellants have found that the method of manufacture does matter; it is possible to make free hyaluronic acid by at least one other method, but the result is not of medical grade, i.e. the product cannot be safely used in the body.

In the parent application, the Examiner had cited three references which appeared to disclose methods of making free hyaluronic acid. These references were U.S. Patent Nos. 4,589,963 (Cipriano), 4,736,024 (Della Valle), and 5,268,079 (Ochoa Gomez). In the Declaration under Rule 132, submitted with the present application, Dr. Beavers described experiments in which he produced a free-acid form of hyaluronic acid, using a procedure which was analogous to those taught by the above references. The results are described in Paragraph 5 of that Declaration. In short, Dr. Beavers was able to use the prior art process to produce a free-acid form of hyaluronic acid, but the product was hemolytic (i.e. harmful to blood cells) and cytotoxic (i.e. harmful to tissues) and therefore not suitable for placement in the body.

The above experiments show that the method of manufacture of hyaluronic acid does matter. When a different method is used to make the product, the result is a different product. Appellants have limited the pending claims to a medical grade hyaluronic acid, which, to the knowledge of Appellants, can be produced only by the specified method.

Because the method of manufacture determines whether or not the product is of medical grade, it follows that, even if a reference mentions a

free-acid form of hyaluronic acid, that disclosure cannot anticipate the present invention unless the reference shows how the product was made. The mere mention of "hyaluronic acid" does not tell the reader whether the product is of medical grade, or whether it is a non-medical grade product produced by the prior art methods.

e) There Is No Disclosure or Suggestion of a Medical Grade Hyaluronic Acid in the Prior Art

In the final rejection, the Examiner held that Schultz met the limitation that the product be suitable for use in the body, because of Schultz's teaching that "hyaluronic acid" can be administered to animals and humans.

But the Examiner has apparently overlooked the fact that Schultz admits that all data in the patent are based on sodium hyaluronate, not hyaluronic acid.

Schultz merely suggests that the free-acid form could be used instead of the salt, and assumes that a free-acid form could be obtained if desired. Schultz gives no teaching or suggestion of how to make the free-acid-form.

It is well established that, in order to be a valid prior art reference, the reference must be enabling, In re Sheppard, 144 U.S.P.Q. 42 (CCPA 1964); In re Borst, 145 U.S.P.Q. 554, 557 (CCPA 1965) ("the criterion should be whether the disclosure is sufficient to enable one skilled in the art to reduce the disclosed invention to practice" (emphasis in original)); In re LeGrice, 133 U.S.P.Q. 365, 372 (CCPA 1962).

Moreover, simply because the name of a compound appears in a reference does not mean that the reference anticipates that compound, In re Wiggins,

James, and Gittos, 179 U.S.P.Q. 421 (CCPA 1973). In the latter case, the court stated:

> The mere naming of a compound, in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference. Id., at 425 (footnote omitted).

Schultz is therefore not an enabling reference for the free-acid form of hyaluronic acid. The patent merely names the substance, but gives no information about how to make it, or how to obtain it. All of the examples of Schultz are based on sodium hyaluronate, not hyaluronic acid.

Appellants' documented experience shows that the free-acid form of hyaluronic acid is not commercially available. Thus, the mere naming of hyaluronic acid, in its free-acid form, in Schultz, cannot be considered an enabling disclosure. A person of ordinary skill could not obtain free hyaluronic acid simply by reading the disclosure of Schultz.

Moreover, Appellants' experiments, documented in the Declarations of Dr. Beavers, show that simply replacing the salt form with any free acid form does not necessarily yield a product that will work satisfactorily in the body. Absent some further disclosure by Schultz, the mere suggestion that the free-acid form could be used cannot render the present invention obvious. Since the method of making the product determines whether it is of medical grade, and since Schultz made no attempt to make or obtain the product, the person of ordinary skill cannot determine, from the Schultz patent, what product to use.

Appellants therefore submit that the Examiner's reliance on Schultz is inappropriate, and that Schultz cannot be deemed to anticipate or suggest the present claimed invention. Appellants therefore submit that the rejection over Schultz should be withdrawn.

f) Surprising Results of the Present Invention

In the final action, the Examiner stated (Paragraph 7) that the final rejection was based, at least in part, on Appellants' alleged failure to show "unexpected results".

Appellants submit that a showing of novelty, utility, and non-obviousness is sufficient, and that an additional showing of "unexpected results" is not necessary or appropriate here.

Stated another way, Appellants submit that the fact that Appellants have synthesized a composition which is not available anywhere is itself an "unexpected" result which merits a patent.

Notwithstanding the above, Appellants have presented further evidence in response to the Examiner's holding, in the Third Declaration of Ellington M. Beavers. Paragraphs 3-9 of that Third Declaration explain the surprising and non-obvious results obtained from the present invention. The details of the Declaration will not be repeated in full here; the following summarizes the important points made therein.

The hyaluronic acid made by the present invention is used to provide a hydrophilic and lubricious coating for articles that are placed permanently or temporarily in the body. The hyaluronic acid is used as part of a bilaminar structure such as is described in U.S. Patent Nos. 4,801,475, 5,023,114, and 5,037,677. The hydrophilic and lubricious top-coat, comprising hyaluronic acid, is joined to a substrate by an intermediate tie-coat which adheres tightly to the substrate, and which is chemically grafted to the top-coat.

As explained in the Third Declaration, in the manufacture of the above-described bilaminar structure, a polymer is added to the tie-coat which will provide the functional groups that will cause chemical grafting

between the top-coat and the tie-coat. Dr. Beavers recognized the desirability of using poly-aziridine (instead of poly-isocyanate) as this polymer, because it is water-soluble, and the poly-isocyanate is not. However, the poly-aziridine does not react with sodium hyaluronate, while it will react with hyaluronic acid in its free form. Thus, it was the need to use poly-aziridine, as the substance that causes the chemical grafting, that motivated Appellants' search for a way to produce a medical-grade hyaluronic acid. The free-acid product invented by Appellants could be used in the body, and could be used with poly-aziridine to provide the desired chemical graft.

The facts outlined above (and stated more fully in the Third Declaration) were not generally known when the invention was made. There was no reason to believe that the free-acid form of hyaluronic acid would have any special utility. Indeed, as shown above, both the academic and business worlds considered hyaluronic acid and sodium hyaluronate to be essentially the same. It was Appellants who found a special (and non-obvious) use for hyaluronic acid. Thus, the claimed product does indeed have unexpected and beneficial results.

Even assuming that the Examiner is correct in requiring a showing of "unexpected results" in this case, Appellants submit that they have fulfilled that requirement. The claimed product is not available commercially, and has unexpected and significant commercial utility.

IX. Conclusion

For the reasons given above, Appellants urge reversal of the Examiner's decision, and request early allowance of the application.

Appellants submit three copies of this Brief.

Respectfully submitted,

William H. Eilberg

William H. Eilberg, Esq.
Registration No. 28,009
420 Old York Road
Jenkintown, PA 19046
215-885-4600

Attorney for Appellants

Appendix

The claims on appeal appear, in numerical order, as follows:

1. A free-acid form of hyaluronic acid, made by the method comprising the steps of:

a) dissolving an alkali-metal salt of hyaluronic acid in water to form a solution,

b) dispersing in said solution an acid capable of producing a pH of 2.2 or lower at concentrations in water at 25° C of 0.01 Normal to 1 Normal,

c) enclosing the dispersion formed in step (b) within a semi-permeable membrane having a molecular weight cut-off at least large enough to pass said acid,

d) dialyzing the dispersion in water while the dispersion is so enclosed, and

e) harvesting free hyaluronic acid from within the semi-permeable membrane,

wherein the free hyaluronic acid harvested in step (e) is suitable for placement permanently or temporarily in the body.

2. The product of Claim 1, wherein the membrane is chosen to be non-ionic.

3. The product of Claim 1, wherein the acid added in step (b) is an acid selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, orthophosphoric acid, and oxalic acid.

4. The product of Claim 1, wherein the semi-permeable membrane is made from a material selected from the group consisting of regenerated cellulose and cellulose esters.

5. The product of Claim 1, wherein the molecular weight cut-off of the semi-permeable membrane is at least twice as great as that needed to

pass the acid added in step (b).

6. The product of Claim 1, wherein the ratio of volume of the water used to dialyze in step (d), to the volume of the hyaluronate solution, is 5:1 or less.

7. The product of Claim 1, wherein the steps are performed at a temperature in the range of about 4-30° C.

8. The product of Claim 1, wherein the dialyzing step is performed until water surrounding the membrane has a predetermined pH.

20. A free-acid form of hyaluronic acid, made by the method comprising the steps of:

a) preparing a solution of sodium hyaluronate in distilled water,

b) mixing into said solution an acid capable of producing a pH of 2.2 or lower at concentrations in water at 25° C in the range of 0.01 Normal to 1 Normal, to produce a mixture,

c) enclosing said mixture in a dialysis bag having a molecular weight cut-off large enough to pass the acid added in step (b),

d) placing the bag in de-ionized water,

e) periodically replacing the de-ionized water with fresh de-ionized water, until the pH of the de-ionized water exceeds 5.0, and

f) harvesting free hyaluronic acid from within the bag,

wherein the free hyaluronic acid harvested in step (f) is suitable for placement permanently or temporarily in the body.

21. The product of Claim 20, wherein the dialysis bag comprises a non-ionic membrane.

22. The product of Claim 20, wherein the acid added in step (b) is hydrochloric acid.

23. The product of Claim 20, wherein the molecular weight cut-off of the bag is 3500.